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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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## INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 17

### Complete If Known

Application Number	10/246,229- 10 667,868
Filing Date	September 17, 2002
First Named Inventor	Stemmer, W.
Art Unit	1655
Examiner Name	Whisenant, E.
Attorney Docket Number	018097-014650US

### U.S. PATENT DOCUMENTS

Examiner	Cite No.	Document Number		Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number	Kind Code <sup>2</sup> (if known)			
JW	AA	US-6,365,408		04-02-2002	Stemmer	
	AB	US-6,361,974		03-26-2002	Short et al.	
	AC	US-6,358,709		03-19-2002	Short et al.	
	AD	US-6,352,842		03-05-2002	Short et al.	
	AE	US-6,323,030		11-27-2001	Stemmer	
	AF	US-6,297,053		10-02-2001	Stemmer	
	AG	US-6,291,242		09-18-2001	Stemmer	
	AH	US-6,287,861		09-11-2002	Stemmer et al.	
	AI	US-6,277,638		08-21-2001	Stemmer	
	AJ	US-6,180,406		01-30-2001	Stemmer	
	AK	US-6,174,673		01-16-2001	Stemmer	
	AL	US-6,171,820		01-09-2001	Short	
	AM	US-6,168,919		01-02-2001	Short	
	AN	US-6,165,793		12-26-2000	Stemmer	
	AO	US-6,132,970		10-17-2000	Stemmer	
	AP	US-6,117,679		09-12-2000	Stemmer	
	AQ	US-6,096,548		08-01-2000	Stemmer	
	AR	US-6,093,873		07-25-2000	Chambon et al.	
	AS	US-6,087,341		07-11-2000	Khavari	
	AT	US-6,087,177		07-11-2000	Wohlstadtter	
	AU	US-6,074,853		06-13-2000	Pati et al.	
	AV	US-6,071,889		06-06-2000	Weiss et al.	
	AW	US-6,057,103		05-02-2000	Short	
	AX	US-6,054,267		04-25-2000	Short	
	AY	US-6,051,409		04-18-2000	Hansen et al.	
	AZ	US-6,030,779		02-29-2000	Short	
	BA	US-6,004,788		12-21-1999	Short	
	BB	US-6,001,574		12-14-1999	Short et al.	
	BC	US-5,976,862		11-02-1999	Kauffman et al.	
	BD	US-5,965,415		10-12-1999	Radman	
	BE	US-5,965,408		10-12-1999	Short	
	BF	US-5,962,258		10-05-1999	Mathur et al.	
	BG	US-5,958,672		09-28-1999	Short	
	BH	US-5,955,358		09-21-1999	Huse	
	BI	US-5,939,250		08-17-1999	Short	
	BJ	US-5,928,905		07-27-1999	Stemmer et al.	

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<sup>2</sup> Applicant's unique citation designation number (optional). <sup>3</sup> Kind Codes of U.S. Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>4</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>5</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>6</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>7</sup> Applicant is to place a check mark here if English language Translation is attached.

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Sheet 2 of 17

### Complete if Known

Application Number	<u>10/246,229-10</u> <u>667,868</u>
Filing Date	<u>September 17, 2002</u>
First Named Inventor	<u>Stemmer, W.</u>
Art Unit	<u>1655</u>
Examiner Name	<u>Whisenant, E.</u>
Attorney Docket Number	<u>018097-014650US</u>

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		Number	Kind Code <sup>2</sup> (if known)			
	BK	US-5,925,749		07-20-1999	Mathur et al.	
	BL	US-5,877,402		03-02-1999	Maliga et al.	
	BM	US-5,871,974		02-16-1999	Huse	
	BN	US-5,866,363		02-02-1999	Piczenik	
	BO	US-5,858,725		01-12-1999	Crowe et al.	
	BP	US-5,851,813		12-22-1998	Desrosiers	
	BQ	US-5,843,643		12-01-1998	Ratner	
	BR	US-5,837,458		11-17-1998	Minshull et al.	
	BS	US-5,834,252		11-10-1998	Stemmer et al.	
	BT	US-5,830,721		11-03-1998	Stemmer et al.	
	BU	US-5,830,696		11-03-1998	Short	
	BV	US-5,824,514		10-20-1998	Kauffman et al.	
	BW	US-5,824,485		10-20-1998	Thompson et al.	
	BX	US-5,824,469		10-20-1998	Horwitz et al.	
	BY	US-5,817,483		10-06-1998	Kauffman et al.	
	BZ	US-5,814,476		09-29-1998	Kauffman et al.	
	CA	US-5,811,238		09-22-1998	Stemmer et al.	
	CB	US-5,808,022		09-15-1998	Huse	
	CC	US-5,795,747		08-18-1998	Henco et al.	
	CD	US-5,783,431		07-21-1998	Peterson et al.	
	CE	US-5,773,267		06-30-1998	Jacobs et al.	
	CF	US-5,770,434		06-23-1998	Huse	
	CG	US-5,763,192		06-09-1998	Kauffman et al.	
	CH	US-5,756,316		05-26-1998	Schellenberger	
	CI	US-5,723,323		03-03-1998	Kauffman et al.	
	CJ	US-5,714,316		02-03-1998	Weiner et al.	
	CK	US-5,698,426		12-16-1997	Huse	
	CL	US-5,679,522		10-21-1997	Modrich	
	CM	US-5,652,116		07-29-1997	Grandi et al.	
	CN	US-5,629,179		05-13-1997	Mierendorf et al.	
	CO	US-5,605,793		02-25-1997	Stemmer	
	CP	US-5,574,205		11-12-1996	Kucheralapati et al.	
	CQ	US-5,571,708		11-05-1996	Yang et al.	
	CR	US-5,556,772		09-17-1996	Sorge et al.	
	CS	US-5,556,750		06-30-1996	Modrich	
	CT	US-5,541,309		06-30-1996	Prasher	

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Sheet **3** of **17**

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Filing Date	September 17, 2002
First Named Inventor	Stemmer, W.
Art Unit	1655
Examiner Name	Whisenant, E.
Attorney Docket Number	018097-014650US

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		Number Kind Code <sup>2</sup> (if known)			
	CU	US-5,523,388	06-04-1996	Huse	
	CV	US-5,521,077	05-28-1996	Khosla et al.	
	CW	US-5,514,568	05-07-1996	Stemmer	
	CX	US-5,512,463	04-30-1996	Stemmer	
	CY	US-5,502,167	03-26-1996	Waldmann et al.	
	CZ	US-5,489,523	02-06-1996	Mathur	
	DA	US-5,470,725	11-28-1995	Borriss et al.	
	DB	US-5,422,266	06-06-1995	Cormier et al.	
	DC	US-5,418,149	05-23-1995	Gelfand et al.	
	DD	US-5,360,728	11-01-1994	Prasher	
	DE	US-5,356,801	10-18-1994	Rambosek et al.	
	DF	US-5,316,935	05-31-1994	Arnold et al.	
	DG	US-5,314,809	03-10-1993	Erich et al.	
	DH	US-5,279,952	01-18-1993	Wu	
	DI	US-5,264,563	11-23-1993	Huse	
	DJ	US-5,234,824	08-10-1993	Mullis	
	DK	US-5,223,408	06-29-1993	Goeddel et al.	
	DL	US-5,187,083	02-16-1993	Mullis	
	DM	US-5,176,995	01-05-1993	Sninsky et al.	
	DN	US-5,169,764	12-08-1992	Shooter et al.	
	DO	US-5,106,727	04-21-1992	Hartley et al.	
	DP	US-5,093,257	03-03-1992	Gray	
	DQ	US-5,043,272	08-27-1991	Hartley	
	DR	US-5,023,171	06-11-1991	Ho et al.	
	DS	US-4,994,379	02-19-1991	Chang	
	DT	US-4,994,368	02-19-1991	Goodman et al.	
	DU	US-4,965,188	10-23-1990	Mullis et al.	
	DV	US-4,959,312	09-25-1990	Sirotkin	
	DW	US-4,816,567	03-28-1989	Cabilly et al.	
	DX	US-4,800,159	01-24-1989	Mullis et al.	
	DY	US-4,683,202	07-28-1987	Mullis	

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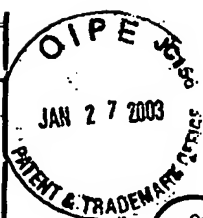
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## INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 4 of 17

### Complete If Known

Application Number	10/246,229 10 667, 863
Filing Date	September 17, 2002
First Named Inventor	Stemmer, W.
Art Unit	1655
Examiner Name	Whisenant, E.
Attorney Docket Number	018097-014650US

FOREIGN PATENT DOCUMENTS								
Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document			Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>2</sup>
		Country Code <sup>3</sup>	Number <sup>4</sup>	Kind Code <sup>5</sup> (if known)				
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Sheet **5** of **17**

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Filing Date	September 17, 2002
First Named Inventor	Stemmer, W.
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Examiner Name	Whisenant, E.
Attorney Docket Number	018097-014650US

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		Country Code <sup>3</sup>	Number <sup>4</sup>	Kind Code <sup>5</sup> (if known)				
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	FM	WO	96/33207		10-24-1996			<input type="checkbox"/>
	FN	WO	97/07205		02-27-1997			<input type="checkbox"/>
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	FT	WO	98/27230		06-25-1998			<input type="checkbox"/>
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### OTHER PRIOR ART -- NON PATENT LITERATURE DOCUMENTS

Examiner Initials *	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
	GF	Adey et al., "Preparation of second-generation phage libraries," <i>Phage Disp. Pept. Proteins</i> , eds. Kay et al., pgs. 277-291 (1996).	
	GG	Andersson et al., "Muller's ratchet decreases fitness of a DNA-based microbe", <i>PNAS</i> , 93: 906-907 (January 1996).	
	GH	Arkin et al., "An Algorithm for Protein Engineering: Simulations of Recursive Ensemble Mutagenesis" <i>Proc. Natl. Acad. Sci. USA</i> , 89(16):7811-7815 (1992).	
	GI	Atreya et al., "Construction of in-frame chimeric plant genes by simplified PCR strategies," <i>Plant Mol. Biol.</i> , 19:517-522 (1992).	
	GJ	Balint et al., "Antibody Engineering By Parsimonious Mutagenesis", <i>Gene</i> , 137(1):109-118 (1993)	
	GK	Bailey, "Toward a Science of Metabolic Engineering", <i>Science</i> , 252: 1668-1680 (1991).	
	GL	Barrett et al., "Genotypic analysis of multiple loci in somatic cells by whole genome amplification", <i>Nuc. Acids Res.</i> , 23(17): 3488-3492 (1995).	
	GM	Bartel et al., "Isolation of New Ribozymes From a Large Pool of Random Sequences", <i>Science</i> , 261:1411-1418 (1993)	
	GN	Beaudry et al., "Directed Evolution of an RNA Enzyme," <i>Science</i> , 257:635-641 (1992).	
	GO	Berger et al., "Phoenix Mutagenesis: One-Step Reassembly of Multiply Cleaved Plasmids With Mixtures of Mutant and Wild-Type Fragments," <i>Anal. Biochem.</i> , 214:571-579 (1993).	
	GP	Berkhout et al., "In Vivo Selection of Randomly Mutated Retroviral Genomes," <i>Nucleic Acids Research</i> , 21(22):5020-5024 (1993).	
	GQ	Bock et al., "Selection of single-stranded DNA molecules that bind and inhibit human thrombin," <i>Nature</i> , 355:564-566 (February 2, 1992).	
	GR	Cadwell et al., "Randomization of Genes by PCR Mutagenesis," <i>PCR Methods and Applications</i> , 2:28-33 (1992).	
	GS	Calogero et al., "In Vivo Recombination and the Production of Hybrid Genes," <i>Microbiology Letters</i> , 76:41-44 (1992).	

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## INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 7 of 17

Complete If Known 10/667,868

Application Number	10/246,229- 10/667,868
Filing Date	September 17, 2002
First Named Inventor	Stemmer, W.
Art Unit	1655
Examiner Name	Whisenant, E.
Attorney Docket Number	018097-014650US

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### OTHER PRIOR ART -- NON PATENT LITERATURE DOCUMENTS

Examiner Initials *	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
EW	GT	Cameron et al., "Cellular and Metabolic Engineering An Overview", <u>Applied Biochem. Biotech.</u> , 38: 105-140 (1993).	
	GU	Caren et al., "Efficient Sampling of Protein Sequence Space for Multiple Mutants," <u>Biotechnology</u> , 12(5):517-520 (1994).	
	GV	Carter, P., "Improved Oligonucleotide-Directed Mutagenesis Using M13 Vectors," <u>Methods in Enzymology</u> , 154:382-383 (1985).	
	GW	Chakrabarty, "Microbial Degradation of Toxic Chemicals: Evolutionary Insights and Practical Considerations", <u>ASM News</u> , 62(3): 130-137 (1996).	
	GX	Chater, "The Improving Prospects for Yield Increase by Genetic Engineering in Antibiotic-Producing Streptomyces", <u>Biotechnology</u> , 8: 115-121 (February 1990).	
	GY	Chen et al., "Tuning the activity of an enzyme for unusual environments: Sequential random mutagenesis of subtilisin E for catalysis in dimethylformamide", <u>PNAS</u> , 90: 5618-5622 (June 1993).	
	GZ	Clackson et al., "Making antibody fragments using phage display libraries," <u>Nature</u> , 352:624-628 (August 15, 1991).	
	HA	Collet et al., "A Binary plasmid System for shuffling combinatorial antibody Libraries," <u>PNAS</u> , 89(21):10026-10030 (1992).	
	HB	Cramer et al., "Combinatorial Multiple Cassette Mutagenesis Creates All The Permutations Of Mutant And Wild-Type Sequences", <u>Biotechniques</u> , 18(2):194-196 (1995)	
	HC	Cramer et al., "Improved Green Fluorescent Protein By Molecular Evolution Using DNA Shuffling", <u>Nat. Biotechnol.</u> , 14(3):315-319 (1996)	
	HD	Cramer et al., "Construction And Evolution Of Antibody-Phage Libraries By DNA Shuffling", <u>Nat. Med.</u> , 2(1):100-102 (1996)	
	HE	Cramer et al., "Molecular Evolution Of An Arsenate Detoxification Pathway By DNA Shuffling", <u>Nat. Biotechnol.</u> , 15(5):436-438 (1997)	
	HF	Cramer et al., "DNA Shuffling Of A Family Of Genes From Diverse Species Accelerates Directed Evolution", <u>Nature</u> , 391(3664):288-291 (1998)	
	HG	Cramer et al., "10(20)-Fold aptamer library amplification without gel purification," <u>Nuc. Acids Res.</u> , 21(18):4410 (1993).	

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Sheet 8 of 17

### Complete if Known

Application Number	10/246,229 10/667,868
Filing Date	September 17, 2002
First Named Inventor	Stemmer, W.
Art Unit	1655
Examiner Name	Whisenant, E.
Attorney Docket Number	018097-014650US

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	HH	Cull et al., "Screening for receptor ligands using large libraries of peptides linked to the C terminus of the lac repressor," <i>PNAS</i> , 89:1865-1869 (March 1992).	
	HI	Cwirla et al., "Peptides on phage: A vast library of peptides for identifying ligands," <i>PNAS</i> , 87:6378-6382 (August 1990).	
	HJ	Daugherty et al., "Polymerase chain reaction facilitates the cloning, CDR-grafting, and rapid expression of a murine monoclonal antibody directed against the CD18 component of leukocyte integrins," <i>Nuc. Acids Res.</i> , 19(9):2471-2476 (1991).	
	HK	Delagrave et al., "Recursive Ensemble Mutagenesis," <i>Protein Engineering</i> , 6(3):327-331 (1993).	
	HL	Delagrave et al., "Searching Sequence Space to Engineer Proteins: Exponential Ensemble Mutagenesis," <i>Biotechnology</i> , 11:1548-1552 (December 1993).	
	HM	Dieffenbach et al., <i>PCR Primer, A Laboratory Manual</i> , Cold Spring Harbor Laboratory Press, pgs. 583-589, 591-601, 603-612, and 613-621 (1995).	
	HN	Dube et al., "Artificial mutants Generated by the Insertion of Random Oligonucleotides into the Putative Nucleoside Binding Site of the HSV-1 Thymidine Kinase Gene," <i>Biochemistry</i> , 30(51):11760-11767 (1991).	
	HO	Evnin et al., "Substrate specificity of trypsin investigated by using a genetic selection", <i>PNAS</i> , 87: 6659-6663 (September 1990).	
	HP	Fang et al., "Human Strand-specific Mismatch Repair Occurs by a Bidirectional Mechanism Similar to That of the Bacterial Reaction", <i>J. Biol. Chem.</i> , 268(16): 11838-11844 (June 5, 1993).	
	HQ	Feinberg et al., "A Technique for Radiolabeling DNA Restriction Endonuclease Fragments to High Specific Activity," <i>Anal. Biochem.</i> , 132:6-13 (1983).	
	HR	Fisch et al., "A Strategy Of Exon Shuffling For Making Large Peptide Repertoires Displayed On Filamentous Bacteriophage", <i>Proc Natl Acad Sci USA</i> , 93(15):7761-7766 (1996)	
	HS	Fullen et al., "Genetic Algorithms and Recursive Ensemble Mutagenesis in Protein Engineering," <i>Complexity Int.</i> 1994, printed from website <a href="http://www.csu.edu.au/ci/vol11/fullen/REM.html">http://www.csu.edu.au/ci/vol11/fullen/REM.html</a> on 12/7/99.	
	HT	Gates et al., "Affinity Selective Isolation Of Ligands From Peptide Libraries Through Display On A Lac Repressor 'Headpiece Dimer'", <i>J. Mol. Biol.</i> , 255(3):373-386 (1996)	
	HU	Ghosh et al., "Arginine-395 Is Required for Efficient in Vivo and in Vitro Aminoacylation of tRNAs by <i>Escherichia coli</i> Methionyl-tRNA Synthetase," <i>Biochemistry</i> , 30:11767-11774 (1991).	

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		Application Number	40/246,229- 101,667,968
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)		Filing Date	September 17, 2002
		First Named Inventor	Stemmer, W.
		Art Unit	1655
		Examiner Name	Whisenant, E.
		Attorney Docket Number	018097-014650US
Sheet	9	of	17

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	HV	Goldman et al., "An Algorithmically Optimized Combinatorial Library Screened by digital Imaging Spectroscopy," <i>Biotechnology</i> , 10:1557-1561 (December 1992).	
	HW	Graf et al., "Random circular permutation of genes and expressed polypeptide chains: Application of the method to the catalytic chains of aspartate transcarbamoylase," <i>PNAS</i> , 93:11591-11596 (1996).	
	HX	Gram et al., "In Vitro Selection and Affinity Maturation of Antibodies From a Naïve Combinatorial Immunoglobulin Library", <i>Proc. Natl. Acad. Sci. USA</i> , 89:3576-3580 (1992).	
	HY	Greener et al., "An Efficient Random Mutagenesis Technique Using An E. coli Mutator Strain", <i>Methods in Molecular Biology</i> , 57:375-385 (1995)	
	HZ	Harlow et al., "Construction of Linker-Scanning Mutations using the Polymerase Chain Reaction," <i>Methods in Mol. Biol.</i> , 31:87-96 (1994).	
	IA	Heda et al., "A simple <i>in vitro</i> site directed mutagenesis of concatamerized cDNA by inverse polymerase chain reaction," <i>Nuc. Acids Res.</i> , 20(19):5241-5242 (1992).	
	IB	Heim et al., "Wavelength Mutations And Posttranslational Autoxidation Of Green Fluorescent Protein", <i>Proc. Natl. Acad. Sci. USA</i> , 91(26):12501-12504 (1994)	
	IC	Hermes et al., "Searching Sequence Space by Definably Random Mutagenesis: Improving the Catalytic Potency of an Enzyme," <i>Proc. Natl. Acad. Sci. USA</i> , 87(2):696-700 (1990).	
	ID	Higuchi et al., "A general method of <i>in vitro</i> preparation and specific mutagenesis of DNA fragments: study of protein and DNA interactions," <i>Nuc. Acids Res.</i> , 16(15):7351-7367 (1988).	
	IE	Ho et al., "DNA and Protein Engineering Using the Polymerase Chain Reaction: Splicing by Overlap Extension," <i>DNA and Protein Eng. Techniques</i> , 2(2):50-55 (1990).	
	IF	Ho et al., "Site-Directed Mutagenesis by Overlap Extension Using the Polymerase Chain Reaction," <i>Gene</i> , 77:51-59 (1989).	
	IG	Hodgson, "The Whys and Wherefores of DNA Amplification," <i>Biotechnology</i> , 11:940-942 (August 1993).	
	IH	Horton et al., "Gene Splicing by Overlap Extension," <i>Methods in Enzymology</i> , 217:270-279 (1993).	
	II	Horton et al., "Gene Splicing by Overlap Extension: Tailor-Made Genes Using the Polymerase chain Reaction," <i>BioTechniques</i> , 8(5):528-535 (May 1990).	

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Sheet 10 of 17

### Complete If Known

Application Number	10/246,220 10/667,868
Filing Date	September 17, 2002
First Named Inventor	Stemmer, W.
Art Unit	1655
Examiner Name	Whisenant, E.
Attorney Docket Number	018097-014650US

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EW	II	Horton et al., "Engineering Hybrid Genes Without the Use of Restriction Enzymes: Gene Splicing by Overlap Extension," <i>Gene</i> , 77:61-68 (1989).	
	IK	Ippolito et al., "Structure assisted redesign of a protein-zinc-binding site with femtomolar affinity", <i>PNAS</i> , 92: 5017-5021 (May 1995).	
	IL	Janczewski et al., "Molecular phylogenetic inference from saber-toothed cat fossils of Rancho La Brea," <i>PNAS</i> , 89:9769-9773 (1992).	
	IM	Jayaraman et al., "Polymerase chain reaction-mediated gene synthesis: Synthesis of a gene coding for isozyme c of horseradish peroxidase," <i>PNAS</i> , 88:4084-4088 (May 1991).	
	IN	Jones et al., "A Rapid Method for Recombination and Site-Specific Mutagenesis by Placing Homologous ends on DNA Using Polymerase Chain Reaction," <i>BioTechniques</i> , 10(1): 62-66 (1991).	
	IO	Jones et al., "Recombinant Circle PCR and Recombination PCR for Site-Specific Mutagenesis Without PCR Product Purification," <i>BioTechniques</i> 12(4):528-534 (1992).	
	IP	Joyce, G. F., "Directed Molecular Evolution," <i>Scientific American</i> , (December 1992).	
	IQ	Kang et al., "Antibody redesign by chain shuffling from random combinatorial immunoglobulin libraries," <i>PNAS</i> , 88(24):11120-11123 (1991).	
	IR	Kellogg et al., "Plasmid-Assisted Molecular Breeding: New Technique for Enhanced Biodegradation of Persistent Toxic Chemicals", <i>Science</i> , 214: 1133-1135 (December 4, 1981).	
	IS	Kim et al., "Cloning and Nucleotide Sequence of the Colib Shufflon," <i>Plasmid</i> , 22:180-184 (1989).	
	IT	Kim et al., "Human Immunodeficiency Virus Reverse Transcriptase," <i>The Journal of Biological Chemistry</i> , 271(9):4872-4878 (1996).	
	IU	Klug et al., "Creating chimeric molecules by PCR directed homologous DNA recombination," <i>Nuc. Acids Res.</i> , 19(10):2793 (1991).	
	IV	Komano et al., "Physical and Genetic Analyses of IncI2 Plasmid R721: Evidence for the Presence of Shufflon," <i>Plasmid</i> , 23:248-251 (1990).	
	IW	Komano et al., "Distribution of Shufflon among IncI Plasmids," <i>J. Bacteriology</i> , 169(11):5317-5319 (1987).	

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## INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 11 of 17

### Complete if Known

Application Number	10/246,229 10/667,862
Filing Date	September 17, 2002
First Named Inventor	Stemmer, W.
Art Unit	1655
Examiner Name	Whisenant, E.
Attorney Docket Number	018097-014650US

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EW	IX	Kramer et al., "Oligonucleotide-directed construction of mutations via gapped duplex DNA," <u>Methods in Enzymology</u> , 154:350-367 (1987).	
	IY	Krishnan et al., "Direct and crossover PCR amplification to facilitate Tn5supF-based sequencing of $\lambda$ phage clones," <u>Nuc. Acids Res.</u> , 19(22):6177-6182 (1991).	
	IZ	Kunkel et al., "Rapid and efficient site-specific mutagenesis without phenotypic selection," <u>Methods in Enzymology</u> , 154:367-382 (1987).	
	JA	Kunkel, "Rapid and efficient site-specific mutagenesis without phenotypic selection", <u>PNAS</u> , 82: 488-493 (January 1985).	
	JB	Leung et al., "A Method For Random Mutagenesis of a Defined DNA Segment Using a Modified Polymerase Chain Reaction," <u>Techniques</u> , 1:11-15 (1989).	
	JC	Levichkin et al., "A New Approach to Construction of Hybrid Genes: Homolog Recombination Method", <u>Mol. Biology</u> , 29(5) part 1: 572-577 (1995).	
	JD	Lewis et al., "Efficient site directed <i>in vitro</i> mutagenesis using ampicillin selection", <u>Nuc. Acids Res.</u> , 18(12): 3439-3443 (1990).	
	JE	Lorberboum-Calski et al., "Cytotoxic activity of an interleukin 2- <i>Pseudomonas</i> exotoxin chimeric protein produced in <i>Escherichia coli</i> ," <u>PNAS</u> , 85:1922-1926 (1988).	
	JP	Lowman, H.B. et al, "Affinity Maturation of Human Growth Hormone by Monovalent Phage Display," <u>J. Mol. Biol.</u> , 234:564-578 (1993).	
	JG	Majumder, K., "Ligation-free gene synthesis by PCR: synthesis and mutagenesis at multiple loci of a chimeric gene encoding OmpA signal peptide and hirudin," <u>Gene</u> , 110:89-94 (1992).	
	JH	Marks et al., "By-passing Immunization, Human Antibodies from V-gene Libraries Displayed on Phage," <u>J. Mol. Biol.</u> , 222:581-597 (1991).	
	JI	Marks et al., "By-Passing Immunization: Building High Affinity Human Antibodies by Chain Shuffling," <u>BioTechnology</u> , 10:779-783 (1992).	
	JJ	Marton et al., "DNA Nicking Favors PCR Recombination", <u>Nucleic Acids Res.</u> , 19(9):2423-2426 (1991)	
	JK	Mayron et al., "Characterization of recombination intermediates from DNA injected into <i>Xenopus laevis</i> oocytes: evidence for a nonconservative mechanism of homologous recombination," <u>Mol. Cell Biol.</u> , 11(6):3278-3287 (1991).	

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## INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 12 of 17

### Complete if Known

Application Number	10/246,229 10/667,868
Filing Date	September 17, 2002
First Named Inventor	Stermer, W.
Art Unit	1655
Examiner Name	Whisenant, E.
Attorney Docket Number	018097-014650US

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✓	JL	McCafferty et al., "Phage antibodies: filamentous phage displaying antibody variable domains," <i>Nature</i> , 348:552-554 (December 6, 1990).	
	JM	Meyerhans et al., "DNA Recombination During PCR," <i>Nucleic Acids Research</i> , 18(7):1687-1691 (1990).	
	JN	Michael, S.F., "Thermostable Ligase-Mediated Incorporation of Mutagenic Oligonucleotides During PCR Amplification," chapter 19 from <i>Methods in Molecular Biology, PCR Cloning Protocols from Molecular Cloning to Genetic Engineering</i> , eds. B. White, Humana Press, totowa, New Jersey, pages 189-195 (1997).	
	JO	Moore et al., "Directed evolution of a <i>para</i> -nitrobenzyl esterase for aqueous-organic solvents", <i>Nature Biotech.</i> , 14: 458-467 (April 1996).	
	JP	Mori et al., "Group II intron RNA-catalyzed recombination of RNA <i>in vitro</i> ," <i>Nuc. Acids Res.</i> , 18(22):6545-6551 (1990).	
	JQ	Mullis et al., "Specific Synthesis of DNA <i>in Vitro</i> via a Polymerase-Catalyzed Chain Reaction," <i>Methods in Enzymology</i> , 155:335-351 (1987).	
	JR	Mullis et al., "Specific Enzymatic Amplification of DNA <i>In Vitro</i> : The Polymerase Chain Reaction," Cold Spring Harbor Symposia on Quantitative Biology, 51:263-273 (1986).	
	JS	Near, "Gene Conversion Of Immunoglobulin Variable Regions In Mutagenesis Cassettes By Replacement PCR Mutagenesis", <i>Biotechniques</i> , 12(1):88-97 (1992)	
	JT	Ner et al., "LABORATORY METHODS: A Simple and Efficient Procedure for Generating Random Point Mutations and for Codon Replacements Using Mixed Oligodeoxynucleotides," <i>DNA</i> , 7(2):127-134 (1988).	
	JU	Nissim et al., "Antibody fragments from a 'single pot' display library as immunochemical reagents," <i>EMBO Journal</i> , 13(3):692-698 (1994).	
	JV	Oliphant et al., "Cloning of Random-Sequence Oligodeoxynucleotides," <i>Gene</i> , 44(2-3):177-183 (1986).	
	JW	Olsen et al., "Hybrid <i>Bacillus</i> (1-3,1-4)-beta-glucanases: engineering thermostable enzymes by construction of hybrid genes," <i>Mol. Gen. Genet.</i> , 225(2):177-185 (1991).	
	JX	Omura, "Philosophy of New Drug Discovery", <i>Microbiol. Rev.</i> , 50(3): 259-279 (September 1986).	
✓	JY	Osuna et al., "Combinatorial mutagenesis of three major groove-contacting residues of <i>Eco</i> RI: single and double amino acid replacements retaining methyltransferase-sensitive activities," <i>Gene</i> , 106:7-12 (1991).	

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## INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet **13** of **17**

### Complete if Known

Application Number	10/246,220 10/667,968
Filing Date	September 17, 2002
First Named Inventor	Stemmer, W.
Art Unit	1655
Examiner Name	Whisenant, E.
Attorney Docket Number	018097-014650US

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EW	JZ	Paabo et al., "DNA Damage Promotes Jumping between Templates during Enzymatic Amplification," <u>J. Biol. Chem.</u> , 265(8):4718-4721 (March 15, 1990).	
	KA	Perlak, "Single Step Large Scale Site-Directed In Vitro Mutagenesis Using Multiple Oligonucleotides", <u>Nucleic Acids Res.</u> , 18(24):7457-7458 (1990)	
	KB	<u>Pharmacia Catalog</u> , pp. 70-71 (1993 Edition).	
	KC	Piepersberg, "Pathway Engineering in Secondary Metabolite-Producing Actinomycetes", <u>Crit. Rev. Biotech.</u> , 14(3):251-285 (1994).	
	KD	Pompon et al., "Protein Engineering by cDNA Recombination in Yeasts: Shuffling of Mammalian Cytochrome P-450 Functions," <u>Gene</u> , 83(1):15-24 (1989).	
	KE	Prasher, "Using GFP to see the light", <u>TIG</u> , 11(8) (August 1995).	
	KF	Prodromou et al., "PROTOCOL, Recursive PCR: a novel technique for total gene synthesis," <u>Protein Engineering</u> , 5(8):827-829 (1992).	
	KG	Rao et al., "Recombination and Polymerase Error Facilitate Restoration of Infectivity in Brome Mosaic Virus," <u>Journal of Virology</u> , 67(2):969-979 (1993).	
	KH	Rapley, "Enhancing PCR Amplification And Sequencing Using DNA-Binding Proteins", <u>Mol. Biotechnol.</u> , 2(3):295-298 (1994)	
	KI	Reidhaar-Olson et al., "Combinatorial Cassette Mutagenesis as a Probe of the Informational Content of Protein Sequences," <u>Science</u> , 241:53-57 (1988).	
	KJ	Rice et al., "Random PCR mutagenesis screening of secreted proteins by direct expression in mammalian cells", <u>PNAS</u> , 89: 5467-5471 (June 1992).	
	KK	Robles et al., "Hydropathy and Molar Volume Constraints on Combinatorial mutants of the Photosynthetic Reaction Center," <u>J. Mol. Biol.</u> , 232:242-252 (1993).	
	KL	Rouwendal et al., "Simultaneous Mutagenesis of Multiple Sites: Application of the Ligase Chain Reaction Using PCR Products Instead of Oligonucleotides," <u>BoiTechniques</u> , 15(1):68-70, 72-74, 76 (1993).	
	KM	Saiki et al., "Diagnosis of sickle Cell Anemia and $\beta$ -Thalassemia with Enzymatically Amplified DNA and Nonradioactive Allele-Specific Oligonucleotide Probes," <u>New England J. of Medicine</u> , 319(9):537-541 (September 1, 1988).	

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## INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 14 of 17

### Complete if Known

Application Number	10/246,229 10/667,368
Filing Date	September 17, 2002
First Named Inventor	Stemmer, W.
Art Unit	1655
Examiner Name	Whisenant, E.
Attorney Docket Number	018097-014650US

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EW	KN	Saiki et al., "analysis of enzymatically amplified $\beta$ -globin and HLA-DQ $\alpha$ DNA with allele-specific oligonucleotide probes," <i>Nature</i> , 324:163-166 (November 13, 1986).	
	KO	Saiki et al., "Enzymatic Amplification of $\beta$ -Globin Genomic Sequences and Restriction Site analysis for Diagnosis of Sickle Cell Anemia," <i>Science</i> , 230:1350-1354 (December 20, 1985).	
	KP	Saiki et al., "Primer-Directed Enzymatic Amplification of DNA with a Thermostable DNA Polymerase," <i>Science</i> , 239:487-491 (January 20, 1988).	
	KQ	Sambrook et al., <i>Molecular Cloning: A Laboratory Manual</i> , Cold Spring Laboratory Press, Cold Spring Harbor, New York (1989).	
	KR	Sambrook et al., <i>Molecular Cloning: A Laboratory Manual</i> , 2nd edition, Cold Spring Harbor Laboratory Press, pages 14.2, 14.34, and 14.35 (1989).	
	KS	Sandhu et al., "Dual Asymmetric PCR: One-Step Construction of Synthetic Genes," <i>BioTechniques</i> , 12(1):14-16 (1992).	
	KT	Scharf et al., "Direct Cloning and Sequence Analysis of Enzymatically Amplified Genomic Sequences," <i>Science</i> , 233:1076-1078 (September 1986).	
	KU	Scott et al., "Searching for Peptide Ligands with an Epitope Library," <i>Science</i> , 249:386-390 (July 20, 1990).	
	KV	Shao et al., "Random-priming <i>in vitro</i> recombination: an effective tool for directed evolution," <i>Nuc. Acids Res.</i> , 26(2):681-683 (1998).	
	KW	Shi et al., "Rapid PCR Construction of a Gene Containing Lym-1 Antibody Variable Regions," <i>PCR Methods and Applications</i> , 3:46-53 (1993).	
	KX	Shuldiner et al., "Hybrid DNA artifact from PCR of closely related target sequences," <i>Nuc. Acids Res.</i> , 17(11):4409 (1989).	
	KY	Sikorski et al., "In Vitro Mutagenesis and Planned Shuffling: From Cloned Gene to Mutant Yeast," <i>Methods in Enzymology</i> , 194:302-318 (1991).	
	KZ	Simpson et al., "Two paradigms of metabolic engineering applied to amino acid biosynthesis", <i>Biochem. Soc. Transactions</i> , vol. 23 (1995).	
	LA	Smith et al., "Unwanted Mutations in PCR Mutagenesis: Avoiding the Predictable," <i>PCR Methods and Applications</i> , 2(3):253-257 (February 1993).	

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## INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 15 of 17

### Complete If Known

Application Number	10/246,229 10/667,868
Filing Date	September 17, 2002
First Named Inventor	Stemmer, W.
Art Unit	1655
Examiner Name	Whisenant, E.
Attorney Docket Number	018097-014650US

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	LB	Smith et al., "Localized sex in bacteria," <u>Nature</u> , 349:29-31 (1991).	
	LC	Steele et al., "Techniques for Selection of Industrially Important Microorganisms", <u>Ann. Rev. Microbiol.</u> , 45: 89-106 (1991).	
	LD	Stemmer, "Rapid Evolution of a Protein in Vitro by DNA Shuffling," <u>Nature</u> , 370:389-391 (1994).	
	LE	Stemmer, "DNA Shuffling by Random Fragmentation and Reassembly: In Vitro Recombination for Molecular Evolution" <u>Proc. Natl. Acad. Sci. USA</u> , 91(22):10747-10751 (1994).	
	LF	Stemmer et al., "Selection of an Active Single Chain FV Antibody from a Protein Linker Library Prepared by Enzymatic Inverse PCR," <u>Biotechniques</u> , 14(2):256-265 (1992).	
	LG	Stemmer, "Searching Sequence Space", <u>Biotechnology</u> , 13:549-553 (1995)	
	LH	Stemmer et al., "Single-Step Assembly Of A Gene And Entire Plasmid From Large Numbers Of Oligodeoxyribonucleotides", <u>Gene</u> , 164(1):49-53 (1995)	
	LI	Stemmer, "The Evolution of Molecular Computation", <u>Science</u> , 270(5241):1510 (1995)	
	LJ	Stemmer, "Sexual PCR and Assembly PCR" <u>Encyclopedia Mol. Biol.</u> , VCH Publishers, New York, pp. 447-457 (1996)	
	LK	Stemmer et al., "Increased Antibody Expression from Escherichia-Coli Through Wobble-Base Library Mutagenesis by Enzymatic Inverse PCR," <u>Gene</u> , 123(1):1-7 (1993).	
	LL	Stemmer et al., "Enzymatic Inverse PCR - A Restriction Site Independent, single-Fragment Method for High-Efficiency, Site-Directed Mutagenesis," <u>Biotechniques</u> , 13(2):214 (1992).	
	LM	Stemmer et al., "Expression of Antibody FV Fragments Specific for a Heavy Metal Chelate Indium Edta In Escherichia-Coli," <u>J. Cell Biochem.</u> , Suppl. 0(15 part G), pg. 217 (1991).	
	LN	Stemmer et al., "A 20-Minute Ethidium Bromide High-salt Extraction Protocol for Plasmid DNA," <u>Biotechniques</u> , 10(6):726 (1991).	
	LO	Stephanopoulos et al., "Metabolic engineering - methodologies and future prospects", <u>Trends Biotech.</u> 11: 392-396 (1993).	

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Sheet **16** of **17**

### Complete If Known

Application Number	40/246,229 10/667,868
Filing Date	September 17, 2002
First Named Inventor	Stemmer, W.
Art Unit	1655
Examiner Name	Whisenant, E.
Attorney Docket Number	018097-014650US

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EW	LP	Stephanopoulos, "Metabolic engineering", <i>Curr. Opin. Biotech.</i> , 5: 196-200 (1994).	
	LQ	Villarreal et al., "A General Method of Polymerase-Chain-Reaction-Enabled Protein Domain Mutagenesis: Construction of a Human Protein S-Osteonectin Gene," <i>Analytical Biochem.</i> , 197:362-367 (1991).	
	LR	Wang et al., "Identification Of Glial Filament Protein And Vimentin In The Same Intermediate Filament System In Human Glioma Cells", <i>Proc. Natl. Acad. Sci. USA</i> , 81(7):2102-2106 (1984)	
	LS	Weber et al., "Formation of Genes Coding for Hybrid Proteins by Recombination Between Related, Cloned Genes in E. Coli," <i>Nucleic Acids Research</i> , 11(16):5661-5669 (1983)	
	LT	Wehmeier, "New multifunctional <i>Escherichia coli</i> - <i>Streptomyces</i> shuttle vectors allowing blue-white screening on XGal plates", <i>Gene</i> , 165: 149-150 (1995).	
	LU	Weissenhorn et al., "Chimerization of antibodies by isolation of rearranged genomic variable regions by the polymerase chain reaction," <i>Gene</i> , 106:273-277 (1991).	
	LV	Winter et al., "Making Antibodies By Phage Display Technology", <i>Ann. Rev. Immunol.</i> , 12:433-455 (1994)	
	LW	Wu et al., "Allele-specific enzymatic amplification of beta-globin genomic for diagnosis of sickle cell anemia," <i>PNAS</i> , 86(6):2757-2760 (1989).	
	LX	Yao et al., "Site-directed Mutagenesis of Herpesvirus Glycoprotein Phosphorylation Sites by Recombination Polymerase Chain Reaction," <i>PCR Methods and Applications</i> , 1(3):205-207 (February 1992).	
	LY	Yolov et al., "Constructing DNA by polymerase recombination," <i>Nuc. Acids Res.</i> , 18(13):3983-3986 (1990).	
	LZ	Yon et al., "Precise gene fusion by PCR," <i>Nuc. Acids Res.</i> , 17(12):4895 (1989).	
	MA	Youvan et al., "Recursive Ensemble Mutagenesis: A Combinatorial Optimization Technique for Protein Engineering," from <i>Parallel Problem Solving from Nature</i> , 2, Manner eds., pp. 401-410 (1992).	
	MB	Zhang et al., "Directed Evolution Of A Fucosidase From A Galactosidase By DNA Shuffling And Screening", <i>Proc. Natl. Acad. Sci. USA</i> , 94(9):4504-4509 (1997)	
	MC	Zhao et al., "Molecular Evolution by Staggered Extension Process (StEP) In Vitro Recombination", <i>Nature Biotech.</i> , 16:258-261 (1998)	

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## INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 17 of 17

### Complete if Known

Application Number	10/246,229 10/667,268
Filing Date	September 17, 2002
First Named Inventor	Stemmer, W.
Art Unit	1655
Examiner Name	Whisenant, E.
Attorney Docket Number	018097-014650US

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### OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS

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	MD	Zoller et al., "Oligonucleotide-directed mutagenesis: a simple method using two oligonucleotide primers and a single-stranded DNA template," <i>Methods in Enzymology</i> , 154:329-350 (1987).	
	ME	Zoller, M.J., "New recombinant DNA methodology for protein engineering," <i>Curr. Opin. Biotech.</i> , 3:348-354 (1992).	
	MP	Biotransformations, Pathogenesis, and Evolving Biotechnology, Program and Abstracts, Pseudomonas '89, American Society for Microbiology and The University of Illinois, 7/9-13/89, abstracts 11-21 to 11-25.	
	MG	Statutory Declaration of Mae Li Gan in Australian Opposition against application 703264.	
	MH	Statutory Declaration of Dr. Gerald Joyce in Australian Opposition against application 703264.	
	MI	Statutory Declaration of Ngare Petit-Young in Australian Opposition against application 703264.	
	MJ	Statutory Declaration of Ruth Bird in Australian Opposition against application 703264.	
	MK	Request for leave to amend the Statement of Grounds and Particulars re: opposition 703264 in Australia (1/25/01).	
	ML	Amended Statement of Particulars re: opposition 703264 in Australia (1/25/01).	
	MM	Opposition Statement in matter of Australian Patent Application 703264 (Affymax Technologies NV), filed by Diversa Corporation on September 23, 1999.	

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